The National Institute on Alcohol Abuse and Alcoholism Strategic Plan 2001-2005

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PREFACE

This document presents the National Institute on Alcohol Abuse and Alcoholism's (NIAAA's) Strategic Plan for the 5-year period 2001–2005. This plan will guide NIAAA in assuring that its resources are invested wisely. It will strengthen coordination within the Institute and across Federal agencies to eliminate costly duplication of programs and services. Determining which areas of research are ready for pursuit, and which ideas merit being moved ahead on an accelerated track, is essential for ensuring continued scientific progress to meet national needs. This plan will support the Institute in responding to the requirements of the Government Performance and Results Act (GPRA). This Act, passed in 1993, requires NIAAA to plan and measure performance in new ways.

Many elements of this plan were developed with input from the National Advisory Council on Alcohol Abuse and Alcoholism, the NIAAA's legislatively mandated advisory board. These elements have been formed, shaped, or influenced by the Council with significant input from scientists in alcohol-related areas as well as other research areas. Council subcommittees accomplished this through program reviews for each of the NIAAA research portfolio areas. In addition, more specific advice on scientific opportunities and public health needs was provided and is reflected in many of the individual plan objectives. The plan also reflects advice from a broad spectrum of sources—researchers, health care providers, over 250 liaison organizations, policymakers, people recovering from alcoholism, their families, and others.

As NIAAA embarks on a new millennium, this document describes its major goals and objectives, strategies for achieving them, and performance indicators that are to be used to report on progress to the public and the Congress.

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On the Frontiers of Knowledge: 30 Years of Alcohol Research

NIAAA's Mission

The mission of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) is to support and conduct biomedical and behavioral research on the causes, consequences, treatment, and prevention of alcoholism and alcohol-related problems.

The NIAAA provides national leadership to the alcohol research community and funds approximately 90 percent of all alcohol research conducted in the United States.

Introduction

The creation in 1970 of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) led to major national interest in research toward solving the problems of alcohol abuse and alcoholism. Although several distinguished scientists had made important contributions to the field prior to that time, funding had been inconsistent and multidisciplinary research on alcoholism was almost nonexistent. With a portfolio that includes internationally respected investigators in a broad range of biomedical and psychosocial disciplines, NIAAA today provides leadership and financial support for approximately 90 percent of all alcohol-related research in the U.S.

An essential impetus to the development of alcoholism research was the acceptance of alcoholism as a medical disorder. This concept has evolved progressively and with considerable controversy over the past 200 years. The disease concept defines alcoholism as an independent disorder characterized by a craving for alcohol—a dependence, or addiction. As such, alcoholism is distinguished from drinking that is merely heavy, problematic, ill advised, or socially unacceptable. True, many alcohol-related problems result from misuse of alcohol by persons who are not alcoholic. Nevertheless, the disease concept has sharpened the focus of alcohol research and has helped remove the stigma from a chronic disorder that is no more inherently immoral than diabetes or heart disease.

In the nearly 30 years since its inception, NIAAA's investment in high-quality biomedical and behavioral research has produced significant results. For example, it is now clear that genes are responsible for approximately half of the risk for alcoholism, making it one of the most heritable of complex disorders. Working from two major lines of evidence, one from the Collaborative Study on the Genetics of Alcoholism (COGA) and the other from intramural studies of a Southwest American Indian tribe, NIAAA-funded scientists have identified several regions—or "hot spots"—on human chromosomes that are likely to contain genes that influence individual susceptibility to alcoholism. Once the genes themselves have been identified, the proteins they encode can be targeted for corrective intervention.

Alcohol affects the brain in many ways. NIAAA-supported investigators have identified the site of transient alcohol-induced changes in the structures of proteins that comprise nerve-cell receptors for neurotransmitters—changes that temporarily modify nerve-cell activity. This research adds to the growing body of evidence that alcohol targets specific protein receptor sites, a finding with significant potential for intervention, both in drug design and eventual clinical application. In the future, this research is expected to provide treatment specialists with even more effective pharmacological tools to help their alcoholic patients recover and avoid relapse.

We also have begun to understand more about the risks to major body organs by excessive alcohol consumption and how to treat alcohol-related medical conditions. For example, discovery of a new research technique that interferes with cellular production of tumor necrosis factor alpha (TNF-alpha) holds promise for reducing liver injury among the more than 2 million Americans with alcoholic liver disease (ALD). Identification of the biological mechanisms of fetal alcohol syndrome (FAS), the country's leading cause of preventable birth defects, suggests potential for pharmacologic interventions and therapeutic measures.

In addition to basic and translational research, NIAAA supports an extensive portfolio of preventive interventions, epidemiology, and treatment research. Genetic predisposition in an individual is not a statement that he or she is destined to become an alcoholic, but a risk factor only. Accordingly, policy, behavioral, and social approaches to prevention remain paramount. Clinical trials of promising new drugs that prevent relapse or inhibit the desire to drink, in combination with behavioral therapy, are ongoing. A growing body of research on treatment has also resulted in improved methods of patient screening and assessment for alcohol disorders. Other examples of rigorous scientific inquiry include prevention studies designed to eliminate drinking in pregnant women, reduce incidence of drunk driving, school- and community-based interventions, and social context and control of drinking in the family and workplace.

Because of the broad implications of adolescent drinking, prevention efforts aimed at this population are a primary focus of the Institute. Recent findings reveal a disturbing correlation between the earlier onset of drinking and the likelihood of life-long alcohol abuse and dependence. More than 40 percent of children who begin drinking before age 15 become alcohol dependent at some time in their lives. Effective prevention in youth may thus be seen as having a payoff in two essential ways. First, it can affect the lives of the persons themselves throughout the most productive periods of their life span. Second, it can be the most effective way to modify risk factors in the children of the next generation by breaking the cycle in the lives of their parents.

Magnitude of the Problem

- More than 100,000 Americans die of alcohol-related causes each year, making alcohol the third leading contributor to mortality related to lifestyle in the U.S. (tobacco is first and diet and activity patterns are second).
- In 1998, the estimated costs of alcohol disorders and their social consequences were $185 billion. Of this sum, direct treatment and health care costs account for 14 percent; reduced worker productivity for 47 percent; and lost productivity due to premature deaths for 20 percent. Costs associated with alcohol-related traffic crashes—the fifth leading cause of death for Americans of all ages—account for 9 percent, as do costs associated with criminal activity. Almost 39 percent of these costs were spread across the U.S. population in the form of increased burdens on government budgets.
- Nearly 53 percent of the adult population of the U.S. (98 million persons aged 18 or older) have a family history of alcoholism or problem drinking. Approximately 6.6 million children under age 18 live in households with at least one alcoholic parent.
- Almost 14 million U.S. adults meet medical criteria for the diagnosis of alcohol abuse or alcoholism.

- Over 30 percent of high school seniors engage in "binge" or heavy drinking (defined as 5 or more drinks on at least one occasion in the past 2 weeks).
- Fetal alcohol syndrome (FAS), a serious disorder affecting brain function, is the leading preventable birth defect in the U.S., with an incidence estimated between 0.5 to 3.0 cases per 1,000 births. A larger number of individuals who do not express the facial features required for a FAS diagnosis nonetheless experiences alcohol-related neurobehavioral deficits caused by prenatal alcohol exposure.

Accomplishing the Mission: Key NIAAA Functions

To achieve its goals, the NIAAA works in partnership with researchers, healthcare and treatment providers, lay organizations, schools, universities, medical schools, communities, businesses, and State, local, and tribal governments—and through them with students, teachers and professors, families, allied healthcare professionals, administrators, employers, and policymakers.

In order to accomplish its mission, the Institute engages in a number of key functions.

- Provide leadership to address critical issues in alcohol research by working closely with the NIAAA National Advisory Council and convening special conferences, workshops, and expert review panels to determine state of knowledge, gaps in knowledge, and research opportunities.
- Fund the highest quality research grants, contracts, and intramural projects to advance knowledge.
- Promote efficient transfer to the private sector of new technology arising from NIAAA-sponsored research to facilitate the commercial development of new diagnostic tools, drugs and other treatment modalities, and related products with significant public health benefits.
- Collaborate closely with lay, professional, and scientific organizations whose missions and goals complement those of NIAAA in order to identify and coordinate crosscutting functions and programs, including research and public health education initiatives.
- Fund research training and career development and mentorship opportunities for promising candidates at the undergraduate and graduate levels in a variety of disciplines, including social, behavioral, biomedical, and life sciences.
- Aggressively monitor adherence to animal research guidelines, human research subject protections, and ensure nondiscrimination for all participants in NIAAA clinical trials.
- Seek advice from State, local, and tribal communities regarding the practical applications of NIAAA-sponsored research findings.
- Provide support for epidemiology, research, evaluation, and dissemination of information to government decision-makers and the public on the consequences of moderate and excessive alcohol consumption.
- Provide key scientific resources to help further research on alcohol-related problems.

NIAAA's Vision: At the Threshold of the New Millennium, New Successes

NIAAA-supported scientists have achieved significant biomedical and behavioral research findings that have substantially furthered our understanding of how alcohol affects the body, behavior, and society. Together, these discoveries have important implications for improving the health and welfare of the American people. They also underscore that proven research programs build cumulatively upon research innovation. Thus, to accelerate the pace of research that has enabled us to come this far, the NIAAA's "vision" for the next five years encompasses seven major research goals. Each goal reflects a core area in which the NIAAA can influence outcomes, even where it does not have direct control. At the same time, the plan underscores that in areas where NIAAA does have direct control—namely, management of its programs, data systems, and workforce—it is as efficient and effective as possible.

NIAAA's strategic plan identifies seven goals.

- **Goal 1. Identify genes that are involved in alcohol-associated disorders.**
- **Goal 2. Identify mechanisms associated with neuroadaptation at multiple levels of analysis (molecular, cellular, neural circuits, and behavior).**
- **Goal 3. Identify additional science-based preventive interventions (e.g., drinking during pregnancy and college-age drinking).**
- **Goal 4. Further delineate biological mechanisms involved in the biomedical consequences associated with excessive alcohol consumption.**
- **Goal 5. Discover new medications that will diminish craving for alcohol, reduce the likelihood of post-treatment relapse, and accelerate recovery of alcohol-damaged organs.**
- **Goal 6. Advance knowledge of the influence of environment on expression of genes involved in alcohol-associated behavior, including the vulnerable adolescent years and in special populations.**
- **Goal 7. Further elucidate the relationships between alcohol and violence.**

Under each goal, the Plan identifies key objectives that, in turn, are supported by nine core strategies described in a separate narrative. These strategies comprise key programs, special initiatives, and specific actions that the NIAAA is pursuing to achieve its vision. Performance indicators, as delineated in annual performance plans, will ensure accountability for results and provide feedback needed to adjust and improve operations over the next five years.

GOAL 1: IDENTIFY GENES THAT ARE INVOLVED IN ALCOHOL-ASSOCIATED DISORDERS

Approximately 50 to 60 percent of the risk for developing alcoholism is genetic. This level of genetic risk is similar to that for other common, serious health disorders, such as adult-onset diabetes, hypertension, asthma, and manic-depressive illness. Although alcoholism is a polygenic disorder (that is, influenced by many genes), the number or identity of genes is not known. In addition, gene-gene interactions as well as the influence of environmental factors are not well understood. Even though excessive consumption may appear outwardly similar among individuals, it is probably the result of the interactions of different sets of genes in different people exposed to different environments.

Scientists involved with the NIAAA-supported Collaborative Study on the Genetics of Alcoholism (COGA) and NIAAA intramural investigators, working independently, have identified several chromosomal regions likely to contain genes associated with alcoholism. These regions reside on human chromosomes l, 2, 4, and 7. In 1998, analysis of these data with newly developed, powerful statistical approaches by geneticists attending the Eleventh International Genetic Analysis Workshop confirmed these findings.

As the NIH-supported, high-resolution mapping of the genome progresses, NIAAA researchers will use this information to help identify which of the hundreds of genes contained in the specified chromosomal locations are implicated in alcoholism. An alternative approach selects a "candidate gene" and uses statistical genetic methods to determine its relationship to alcoholism; this approach has been used to identify protective genetic variants of aldehyde dehydrogenase (ALDH) and alcohol dehydrogenase (ADH). The genetic and clinical data collected by COGA are available to qualified investigators in order to expedite discovery.

Genes direct the synthesis of proteins, and it is the proteins that drive and regulate critical chemical reactions throughout the human body. Genetics affects virtually every facet of alcohol research, from neuroscience (e.g., identification of neurotransmitter and receptor proteins that are involved in alcohol-related behavior) to fetal alcohol syndrome (e.g., discovery of a specific protein that may be an embryonic biomarker). For those individuals who develop alcohol-related problems, identification of the roles of specific proteins in critical chemical pathways may eventually result in therapeutic genetic interventions.

Recent Scientific Advances

Alcoholism

NIAAA-supported investigators are continuing to identify regions of particular chromosomes wherein genes reside that are associated with the clinical signs and symptoms of alcoholism, both in population isolates and in samples more characteristic of the general population. Interesting findings have been reported for selected phenotypes that are associated with alcoholism but not diagnostic of alcoholism, for example, smoking and electrophysiological characteristics. Phenotypes are observable properties, traits, or physical appearances, some of which may result from the interaction of genes with environmental factors. It is anticipated that high-resolution mapping will enable researchers to pinpoint which of the hundreds of genes contained in identified chromosomal regions are linked to alcoholism.

Rodent Models

Nonhuman animals provide a more readily manipulated and relatively inexpensive model for genetic identification. Animal models have been developed that enable researchers to perform controlled analy-

ses of genetically influenced biological traits and behaviors, such as alcohol consumption and preference, innate sensitivity or tolerance to alcohol, and metabolic rate of alcohol elimination. NIAAA-funded scientists have applied molecular-biology techniques to develop gene knockout mice in which genes associated with traits that might influence alcohol-related behavior have been inactivated. For example, scientists have studied the neural and behavioral responses to alcohol in mice with knockouts of the following genes: serotonin 5HT-1B receptor, GABA-A receptor, dopamine receptors, beta-endorphin, and protein kinase C isoforms. Other studies in mice have found that different genes influence alcohol consumption in males and females, suggesting that different genes may also influence alcoholism in men and women.

Extensive selective breeding of animals has also produced genetic lines differing in several alcohol-related traits. This approach has enabled chromosomal locations to be identified for a number of alcohol-related behaviors, including drinking preference, sedation, ataxia, and withdrawal. Examples of candidate genes being investigated by molecular genetics techniques are serotonin 1B, dopamine D2 receptor, tryptophan hydroxylase, and neuropeptide Y.

Invertebrate Models

Genetic studies in the fruit fly (*Drosophila*) have resulted in precise information about genes and specific proteins that have relevance to alcohol-related behavior in man because humans and fruit flies share many genes. NIAAA-funded researchers have linked a specific gene mutation to increased sensitivity to the effects of alcohol in the fruit fly. Further research revealed that these flies produced less of a critical intracellular signaling molecule, cAMP. While researchers have known for some time that changes in cAMP somehow are correlated with alcoholism in humans, the significance of this phenomenon was not clear. It is now possible to explain how changes in cAMP levels can cause increased sensitivity to alcohol.

Goal 1: Objectives

Over the next five years, NIAAA plans to focus on three objectives.

- **Objective 1. Identify and/or increase knowledge of genes in mice, rats, and invertebrates that are responsible for altered responses to alcohol.**
- **Objective 2. Identify and/or increase knowledge of genes associated with alcoholism-related disorders in humans.**
- **Objective 3. Strengthen the technical infrastructure required to identify genes that are associated with alcohol-related responses.**

Goal 2: Identify Mechanisms Associated With Neuroadaptation at Multiple Levels of Analysis (Molecular, Cellular, Neural Circuits, and Behavior)

The mechanisms by which alcohol produces intoxication, reinforcement of continued drinking, dependence, withdrawal upon cessation of drinking (discomfort of abstinence), and relapse are primarily located in the brain. Recent progress in neuroscience research has yielded information critical to characterizing some of the cellular and molecular processes and has helped associate these processes

with the behavioral and physiologic manifestations of alcohol use and abuse. For example, NIAAA-supported investigators have identified the site of alcohol-induced changes in the structure of proteins that comprise nerve-cell receptors for neurotransmitters—changes that temporarily modify nerve-cell activity. This research adds to the growing body of evidence that alcohol targets specific protein receptor sites in the brain.

One of the best ways to identify mechanisms associated with neuroadaptation to alcohol is to integrate molecular, cellular, neurocircuitry, neural network, and whole-animal levels of analysis of various aspects of neuroadaptation. Development of appropriate and well-characterized animal models and human studies of alcohol-related phenomena is necessary for success. Human studies need to address recent and chronic history of alcohol consumption; psychiatric comorbidity; age, gender, race and ethnicity; family history of alcohol-related behavior; and whether the sample is collected from population isolates or is more representative of the general population. Animal models already developed for specific alcohol-related phenomena include invertebrates, rodents, and non-human primates, with different models being selected on the basis of specific research questions. Since each organism and each model has strengths and weaknesses, continued investment in the development of human and animal models of alcohol-related phenomena is required for successful integration of neuroscience information.

Recent Scientific Advances

Specific Brain Circuits Mediate Reinforcing Effects of Alcohol

A complex, negative feedback system within the mesolimbic dopamine system (ventral tegmental area, nucleus accumbens, central nucleus of the amygdala, and prefrontal cortex) is involved in the regulation of alcohol consumption.

Alcohol Reinforcement is Mediated by the Interaction of Multiple Neurotransmitters

NIAAA-supported investigators have determined that the reinforcing effects of alcohol in dependent and non-dependent animals involves the neurotransmitters dopamine, opioid peptides, gamma-aminobutyric acid (GABA), glutamate, and serotonin (5-HT). Moreover, it appears that alcohol-dependent animals experience the reinforcing properties of alcohol differently than do nondependent ones.

Evidence for Alcohol-Altered Receptors

NIAAA-funded scientists have identified a site of alcohol-induced changes in the structure of proteins that comprise nerve-cell receptors for the inhibitory neurotransmitters GABA and glycine. This knowledge can be of assistance in future medication development.

Alcohol Consumption and Neuropeptide Y Levels

NIAAA-supported investigators reported that mice lacking the neuropeptide Y gene consumed more alcohol and were more resistant to alcohol-induced sedation than their normal counterparts. Conversely, mice genetically engineered to make increased amounts of neuropeptide Y in many brain regions consumed less alcohol but were more sensitive to alcohol-induced sedation. These findings suggest that neuropeptide Y and its receptors play a role in regulating alcohol consumption and sensitivity in mice, and by implication, in humans. Such a role was previously unsuspected.

Goal 2: Objective

Over the next five years, NIAAA plans to focus on the following major objective.

Objective 1. Advance knowledge of the mechanisms associated with alcohol-related phenomena of sensitization, tolerance, dependence, withdrawal, recovery, and relapse at the molecular, cellular, neurocircuitry, neural network, and whole-animal levels.

Goal 3: Identify Additional Science-Based Preventive Interventions

The goal of science-based preventive interventions is to reduce alcohol-related problems. This may be achieved by focusing on the environment in which alcohol is distributed, sold, and consumed (e.g., policies that affect availability of alcohol) or on particular groups and individuals at excess risk of alcohol misuse. Identifying contributors to risk (i.e., risk factors) that may be malleable is a helpful first step in establishing successful preventive intervention programs. Examples of such risk factors include environmental permissiveness, peer influences, and the absence of strong refusal skills to avoid adolescent alcohol use and abuse.

It is useful to distinguish alcohol-related problems as acute or chronic. Acute problems are those that arise from drinking events that result in temporary but significant alcohol-related impairment in the individual (for example, reduced hand-eye coordination and increased impulsiveness). Examples of acute alcohol-related problems include injuries and death due to motor vehicle crashes; falls, fire, and drowning; domestic violence; and unprotected sexual activity. In contrast, chronic problems arise from long-term excessive alcohol consumption and include alcohol dependence and a spectrum of health consequences, such as alcoholic liver disease and alcohol-associated cognitive impairments. The challenge is to find those strategies that can reduce specific problem outcomes including those that result from long-term drinking.

Effective prevention intervention in youth is seen as particularly important, especially since there is a significant correlation between the earlier onset of drinking and the likelihood of life-long alcohol abuse and dependence.

Fetal alcohol syndrome (FAS) is one of the leading causes of mental impairment in the United States, and it has been considered the leading preventable birth defect given that the potential for the occurrence of the disorder is eliminated with abstention from alcohol during pregnancy. However, the challenge of preventing FAS is considerable for several reasons. Among these is the fact that considerable alcohol-related insult may be inflicted on the developing embryo during the first month of pregnancy, a time when the mother may not yet know that she is pregnant. An Institute of Medicine study developed recommendations on research approaches to FAS prevention with three levels of focus: universal prevention efforts, targeted to the entire population; selected prevention efforts to women in high risk groups; and indicated prevention targeted to high risk individuals (for example, women who previously have given birth to an FAS child). These approaches await implementation and validation.

Recent Scientific Advances

Innovative intervention research supported by the NIAAA is already demonstrating preventive effects and favorable cost-benefit results. Recent scientific advances promise to reduce the risk for alcohol disorders in vulnerable populations and to help contain the monetary costs associated with them.

Alcohol Use and Public Policies

Alcohol consumption and alcohol-related problems can be influenced by various kinds of laws and regulations. A substantial body of econometric research has established that consumption of beer, wine, and distilled spirits declines in response to increases in the prices or taxes associated with these beverages. Higher prices or taxes for alcoholic beverages are also associated with improvements in a wide variety of adverse outcomes, including the probability of frequent beer consumption by young people, probability of adults drinking five or more drinks on a single occasion, death rates from cirrhosis and motor vehicle crashes, frequency of drinking and driving, and some categories of violent crime.

Recent evidence suggests potentially important differences in the price-responsiveness of different categories of drinkers. One study found that the heaviest-drinking five percent of drinkers (accounting for 36 percent of all alcohol consumed) exhibited no significant consumption changes in response to variations in beverage prices. Another study found significant price responsiveness among some heavy drinkers, but found that those who were most ill-informed about health problems associated with heavy drinking were essentially unresponsive to price changes. These findings suggest the need for further research to characterize in detail the effects of policies on specific behaviors and among various subpopulations.

A critical public policy need is to identify ways to reduce further the toll of alcohol-related motor vehicle crashes. Motor vehicle crashes are the leading cause of death among Americans aged 1 to 24 years, and alcohol-related fatalities accounted for 38 percent of total traffic fatalities in 1998. Reductions in alcohol-related traffic crashes are associated with many policy measures, including administrative revocation of licenses for drinking and driving, an increase in the minimum legal drinking age to 21, lower maximum legal blood alcohol levels for young drivers and adults, and (as noted above) higher taxes or prices on alcoholic beverages. Recent research has found that setting lower legal blood alcohol limits effectively reduces fatal alcohol-related crashes among adolescents, based on analyses using the proxy measure of single-vehicle nighttime fatal crashes. Studies have also found that raising the minimum legal drinking age to 21 years was associated with reductions in alcohol consumption and traffic fatalities among young people.

Community-Based Interventions

Over the past decade, community-based prevention studies focusing on alcohol have received increasing attention. These studies have shown that variations in alcohol use across communities cannot be explained fully in terms of known individual characteristics. Rather, community structures, institutions, and policies interact to affect drinking and the risk for alcohol problems.

Several community-based alcohol prevention projects have achieved significant results in raising public awareness and support for prevention of alcohol problems, while reducing alcohol sales to youth, underage drinking, drinking and driving, related driving risks, and traffic deaths and injuries. NIAAA-funded researchers also have combined innovative school curricula, peer leader programs, parent involvement and education, and community task forces in successful interventions.

College Campus Interventions

Alcohol abuse among college students, many of whom are under the minimum legal drinking age, is a major health problem on college campuses. The highest-risk campus groups are fraternities and sororities. Recently, it has been estimated that college students spend $5.5 billion on alcohol, more than they spend on soft drinks, juice, milk, tea, coffee, and books, combined. Although there is a general lack of

knowledge on the effectiveness of college campus interventions, there has been recent interest in this area. NIAAA-funded research has shown that brief motivational counseling in the form of normative feedback to students can significantly reduce alcohol-related problems among students known to engage in hazardous drinking. Normative feedback is a process in which an individual is informed how his or her behavior compares to that of similarly situated peers. In related findings, challenging students' false expectancies about the positive benefits of drinking can also reduce their alcohol consumption, at least temporarily. Teaching students cognitive/behavioral skills that help them monitor and moderate their drinking has proved to be more effective in reducing excessive consumption than providing students with general information and education about alcohol-related problems.

Primary Health Care Interventions

Research suggests that involvement of primary health care providers can enhance the efficacy of preventive interventions for youth. In one study, STARS (Start Taking Alcohol Risks Seriously), the intervention coupled self-instructional modules and audiotapes with health consultations with primary care physicians or nurses. The findings showed significant benefits, especially for youth with prior signs of alcohol-related problems. Similar results were found in preliminary data from a randomized trial of 3,300 fifth and sixth graders in another primary health care intervention.

Workplace Interventions

The high prevalence of alcohol problems among adults in the labor force indicates that worksite interventions have the potential to reduce significantly the adverse health and safety consequences of alcohol abuse. NIAAA-funded investigators have established that permissive norms regarding work-related drinking are predictive of on-the-job drinking patterns; corporate restructuring or downsizing exerts an adverse impact on drinking in the workplace; and feelings of diminished worth among employees, especially those whose work demands or social interactions are minimal, result in increased drinking and alcohol-related problems.

Goal 3: Objectives

Over the next five years, the following eight objectives are to be emphasized.

Objective 1. Increase knowledge relevant to the efficacy of community- and school-based interventions to larger urban communities and diverse ethnic and underserved high-risk populations.

Objective 2. Increase understanding of the effects of alcohol advertising on youth and the impact of media-based (radio, TV) preventive interventions.

Objective 3. Further knowledge of the impact of alcohol price/tax changes on various subgroups of drinkers and types of drinking (e.g., heavy vs. moderate).

Objective 4. Study whether geospatial modeling can increase the effectiveness of preventive interventions by targeting specific geographical locations.

Objective 5. Examine environmentally focused interventions to prevent alcohol abuse/problems on college campuses.

Objective 6. Develop and evaluate worksite preventive interventions (including policy changes).

Objective 7. Develop and evaluate family-based preventive interventions.

Objective 8. Develop and evaluate interventions to prevent FAS and other alcohol-related birth defects.

GOAL 4: FURTHER DELINEATE BIOLOGICAL MECHANISMS INVOLVED IN THE BIOMEDICAL CONSEQUENCES ASSOCIATED WITH EXCESSIVE ALCOHOL CONSUMPTION

Alcohol consumption induces a variety of widespread pathologies on many tissues and organs of the body. The result is a diverse array of medical consequences that are not mutually exclusive and range from organic brain damage, to liver cirrhosis, to modifications in the process of wound healing. For example, alcoholic liver disease can lead to systemic metabolic and physiologic changes that alter neurological function. Levels of alcohol consumption determine physiologic changes in organ function. Excessive consumption of alcohol contributes to heart and cardiovascular disease, while light drinking may have some benefits for cardiac health. Excessive consumption, particularly of a chronic nature, depresses immune system function, resulting in increased susceptibility to bacterial and viral infections, such as tuberculosis and hepatitis C. Chronic alcohol consumption is also implicated in an increased risk for certain cancers (e.g., esophageal, oral, liver, and breast cancer).

Alcohol perturbs a variety of hormonal functions, and depending upon the duration of exposure, it may activate or blunt particular components. Endocrine pathways generally recognized as being susceptible to alcohol's interactions include the hypothalamic-pituitary-adrenal (HPA) axis and the opiomelanocortinergic system, but further investigation is revealing that alcohol's impact is more widespread. These endocrine perturbations produce or contribute to a variety of medical conditions, notably reproductive disorders, osteoporosis, and breast cancer. Recently, interest has been focused upon the role of hormones and their receptors in regulating alcohol consumption in humans and animals. Particular peptides, including neuropeptide Y, beta-endorphin, corticotropin releasing factor, and angiotensin II, represent fertile areas of future exploration.

Maternal alcohol consumption during pregnancy can produce developmental problems in offspring. Fetal alcohol syndrome (FAS), associated with excessive alcohol consumption, refers to a constellation of birth defects including facial abnormalities, low birth weight, and mild to severe brain damage leading to mental retardation and/or behavioral problems. FAS remains the leading preventable cause of mental retardation in the U.S. Partial manifestations of FAS are associated with lower levels of consumption; for every child with FAS, there are many less severely affected children.

Recent Scientific Advances

Fetal Alcohol Syndrome

Animal models of FAS provide a unique insight into the etiology and pathogenic mechanisms of the syndrome. Recent animal studies have elucidated temporal and regional vulnerability for alcohol-related effects on development, especially for the brain. NIAAA-sponsored scientists have made advances in

identifying potential mechanisms by which alcohol may cause FAS. Among these is the proposed inhibition by alcohol of alcohol dehydrogenase-catalyzed retinoic acid synthesis. Retinoic acid is a prominent regulator of differentiation during vertebrate embryogenesis. Alcohol consumption may result in decreased levels of retinoic acid in the cranial mesenchyme, derived from cranial neural crest. Neural crest cells are crucial embryological cells that differentiate into a wide variety of cell types, including nerve cells of the brain and spinal cord as well as facial bone and cartilage. A second mechanism of developmental pathology involving neural crest cells may occur when alcohol exposure triggers an abnormal cell-death pathway in neural crest cells, resulting in severe craniofacial and myocardial deformities. NIAAA-supported scientists have found *in vitro* evidence that oxygen-free radicals, including those induced by alcohol, can lead to neural crest cell death. Treating alcohol-exposed neural crest cells with free-radical scavengers significantly improved the cells' viability. Moreover, molecules capable of neutralizing free radicals reduce or mitigate harmful effects on the neural crest, a finding that suggests potential for pharmacological interventions and therapeutic measures.

Alcoholic Liver Disease

Alcoholic liver disease (ALD) is a major cause of cirrhosis and a leading cause of liver failure resulting in a need for liver transplantation in the U.S. and the Western world. Alcohol researchers have been using animal models to study pathogenic mechanisms and possible treatments. Alcohol has been shown to trigger activation of the liver's Kupffer cells, which produce tumor necrosis factor (TNF), a mediator of liver pathogenesis. NIAAA-funded investigators are studying the effects of reducing TNF levels. Experimental treatment with anti-TNF antibodies significantly reduces inflammation and tissue death in the liver, offering a potential therapy. Investigators have also developed a gene-based therapeutic approach using an enhanced antisense oligonucleotide, and in so doing, improved *in vitro* success rates for inhibition of TNF-alpha production. Researchers have developed TNF-R1 knockout mice that do not express TNF, and these animals are refractory to ALD.

Neuroendocrine Peptide Regulation of Alcohol Consumption

In addition to the classical neurotransmitters, many neuropeptides have been identified and are believed to act as modulators of neurotransmission. Although many actions of alcohol on neurotransmitters have been reported, the potential role of various peptides is a current area of research. For example, Neuropeptide Y (NPY), a hormone that can function as a neurotransmitter in the brain, is known to stimulate appetitive behaviors. Recently, NIAAA-funded scientists reported that mice rendered NPY-deficient by elimination of the NPY gene consumed more alcohol and were less sensitive to the sedative effects of alcohol than controls. Conversely, mice genetically altered to produce abnormally high levels of NPY showed a lower preference for alcohol and were more sensitive to alcohol's sedative effects. These findings suggest that NPY is part of the neural circuits involved in responses to alcohol.

Stress and Alcohol

Studies indicate that some individuals consume alcohol as a means of coping with economic stress, job stress, and marital problems, often in the absence of social support, and that the more severe and chronic the stressor, the greater the alcohol consumption. While research indicates that alcohol can induce the stress response, a clear association between stress, drinking behavior, and development of alcoholism in humans has yet to be established. Recently, much attention has been directed at understanding the role of the nonneuroendocrine corticotropin-releasing factor (CRF) system in the

mediation of behavioral and physiological responses to stress. The CRF system is thought to play an essential role in mobilizing the body's response to stress, even perceived stress, across a highly complex, integrated network involving brain, adrenal system, and cardiovascular system.

Alcohol and the Cardiovascular System

Research has revealed an association between moderate alcohol consumption and a lower risk for coronary heart disease. This association does not mean that alcohol itself is the cause of the lower risk. NIAAA-funded scientists are elucidating the cellular and molecular mechanisms associated with the moderate consumption of alcohol. Current activities are concentrating on moderate alcohol consumption and plasma lipoprotein profiles and blood coagulatory/fibrinolytic pathways. It is generally accepted that alcohol increases plasma high-density lipoprotein cholesterol (HDL) levels. However, changes in HDL and low-density lipoprotein cholesterol (LDL) levels explain only about half of the observed effects of alcohol. Researchers are also studying how alcohol alters vascular hemostasis via changes in activity, level, and interaction between components of the fibrinolytic pathway.

Alcohol-Induced Impairments of the Immune System

Excessive or prolonged consumption of alcohol can result in more frequent and severe infections. Studies in human cell systems and animal models have shown that alcohol-induced immune system dysfunction can be traced to a specific stage in the immune process when the body first encounters pathogenic organisms. Specific immune cells, designated T lymphocytes, normally respond to foreign microorganisms along two general pathways: cell-mediated immunity, and humoral (or antibody) immunity. The types of immune responses can be identified and studied according to their pattern of cytokine (chemical messengers) production. NIAAA-supported researchers have discovered that after chronic alcohol exposure, cytokine profiles are shifted toward antibody responses and cell-mediated immunity is diminished. The result of this shift towards antibody responses is that the immune system of an alcohol-affected individual may be deficient in fending off certain bacterial (tuberculosis), fungal, and parasitic pathogens and be hyper-responsive to toxins (tetanus) and lung conditions such as asthma. By understanding how alcohol alters the immune system, scientists can develop medications to help normalize the malfunctioning immune defenses.

Goal 4: Objectives

Although research is advancing our understanding of what biological mechanisms are involved in alcohol-induced organ damage and recovery, as well as the systemic manifestations of alcohol consumption, a major investment in further research is needed to address the complex objectives to be elucidated. This research is directed and has the potential to identify targets for medication development.

Over the next five years, NIAAA will focus on the following seven objectives.

Objective 1. Increase understanding of interactions that modulate alcohol consumption, including involvement of neurotransmitters and their receptors, hormones, peptides, and signal-transduction pathways.

Objective 2. Advance knowledge of susceptibility to alcohol-induced pathogenesis for neonatal, adolescent, adult, and aged tissues and organs, with specific emphasis on the brain.

Objective 3. Increase knowledge of molecular mechanisms of pathogenesis for alcohol-induced liver disease and pancreatitis.

Objective 4. Increase knowledge of mechanism(s) of alcohol-induced alteration of immune function, which results in (1) increased susceptibility to infection and (2) enhanced progression of pathogenesis (e.g., liver cirrhosis and hepatocellular carcinoma due to infectious diseases such as hepatitis C).

Objective 5. Further elucidate biological mechanisms associated with the interactions among neuropeptides, alcohol consumption, and stress.

Objective 6. Investigate alcohol-induced alterations in cell-death pathways that result in pathogenesis and teratogenesis.

Objective 7. Increase knowledge required for the development of treatments to reduce alcohol-related morbidity and mortality arising from immune system dysfunction, especially in the elderly.

Goal 5: Discover New Medications to Diminish Craving for Alcohol, Reduce Likelihood of Posttreatment Relapse, and Accelerate Recovery of Organ Function

Some of the most compelling questions about treatment have to do with what therapies work. Some studies have shown significant reductions in drinking following treatment with behavioral therapies that have been extensively tested and refined. Other studies, involving brief interventions in primary care settings, have proved to be effective in reducing alcohol consumption in persons drinking at levels associated with negative health consequences. Because many individuals continue to experience problems with alcohol after treatment, there is a need to further improve treatment efficacy.

Developing effective pharmacotherapies (medication treatment) for alcoholism has emerged as a top priority for NIAAA. Development of medications for treatment of alcohol-related disorders relies on research that explores the ways in which the diverse behavioral effects of alcohol may be coupled to specific alcohol-induced changes in the brain. Specific targets of alcohol in the brain are being characterized, and the adaptive mechanisms leading to alcohol dependence identified. Studies involving selectively bred animals, genetically engineered animals, advanced behavioral analyses, and newly developed bioanalytical methods have provided important new information about many neurochemical pathways in which alcohol interacts and which appear to be involved in maintaining the motivation to drink. Together with findings from other research exploring the biology of alcohol tolerance, withdrawal, and impaired control over drinking, these studies have suggested a range of possibly beneficial compounds for treating alcoholism.

An example of such a compound is naltrexone. This drug is an opioid antagonist, which acts on opioid receptors in the brain. In 1994, NIAAA-supported research resulted in U.S. Food and Drug Administration (FDA) approval of naltrexone as a useful treatment for alcoholism when coupled with intensive behavioral therapy. Other opioid antagonists are currently being examined. In addition to naltrexone, another promising agent for treating alcoholism is acamprosate. Clinically tested and used successfully in Europe for several years, acamprosate has been shown to maintain abstinence. NIAAA has established a multi-site clinical trial to continue evaluation of naltrexone and acamprosate, singly and together, and to determine how the medications augment state-of-the-art behavioral therapy for alcoholism.

With rapid advances in understanding a number of alcohol-related phenomena, including reduction in alcohol consumption, craving and relapse, signs and symptoms accompanying acute and protracted withdrawal, alcohol-induced cognitive dysfunction, intoxication, and various endpoints of organ damage, an unprecedented opportunity exists to develop and evaluate potential new medications for eventual clinical use, as well as further develop and evaluate compounds that already show clinical potential based on preclinical data.

Recent Scientific Advances

Medications that Modulate/Suppress the Desire to Drink

Over the past five years, progress has been made in finding medications that diminish the desire to drink (sometimes referred to as "anticraving" medications). Various studies have focused on those neurotransmitter and receptor systems that have been implicated. Research on dopaminergic, serotonergic, gamma-aminobutyric acid (GABAergic) systems, glutamate *N*-methyl-D-aspartate (NMDA), and opiate receptors has opened up new approaches into the pharmacotherapy for alcoholism. In addition to the opioid antagonists, naltrexone and nalmefene, which have shown promising results, the compound acamprosate has been shown to suppress alcohol intake and relapse in alcoholics and animals without an alteration in alcohol toxicity. The mechanisms underlying acamprosate's effects are still being investigated. With the paucity of medications to reduce the desire to drink, a high priority is for the development of new compounds in this area.

Medications to Treat Acute Alcohol Withdrawal

A highly variable range of signs and symptoms characterizes acute alcohol withdrawal. These signs and symptoms may be mild (for example, sweating, tachycardia, hypertension, tremors, and anxiety) or more serious (for example, seizures and delirium tremens). Acute alcohol withdrawal is widely believed to involve disturbance of one or more neuronal and hormonal systems, including noradrenergic hyperactivity, alterations in gamma-aminobutyric acid (GABA)-benzodiazepine receptors, elevated activity of the hypothalamic-pituitary-adrenal (HPA) axis, and changes in the NMDA glutamate receptors.

Recent research has suggested that the "kindling" effect (or increased reactivity with repeated bouts of excessive alcohol consumption) may intensify subsequent withdrawals.

For more than two decades, benzodiazepines have been the most widely used class of medications for managing alcohol withdrawal. Recent studies have focused on benzodiazepine dosing strategies to minimize withdrawal. Other medications being explored in the management of withdrawal symptoms include NMDA antagonists, dopaminergic agents, and calcium channel antagonists. Their effectiveness in the clinic has yet to be established.

Medications to Treat the Protracted Withdrawal Syndrome

The protracted withdrawal syndrome, also known as protracted abstinence or late withdrawal, is in the very early stages of research. The lack of agreement on distinctive signs and symptoms and the duration of the syndrome has hampered pharmacological treatment. Some of the purported symptoms include anxiety, irritability, hostility, depression, insomnia, fatigue, and craving. Expanded research is needed to determine the efficacy of new pharmacotherapies to reduce the signs and symptoms associated with the protracted withdrawal syndrome.

Medications to Improve Alcoholism-Associated Cognitive Dysfunction

A significant need exists to develop treatments for the prevention and amelioration of the cognitive disturbances and structural brain damage associated with alcoholism. Recent studies have suggested that some medications can improve memory to a clinically meaningful degree in some patients with alcohol-induced amnesia. Among chronic excessive drinkers, there is a wide spectrum of cognitive disturbances associated with chronic drinking, ranging from mild impairments, such as reduced attention span and visuospatial abilities, to severe amnesia, dementia, and psychosis. Medications to improve cognitive function in alcoholics not only promise to enrich their quality of life but also to reduce the costs of long-term institutionalization that is required in more severe cases.

Gene Therapy

NIAAA-supported researchers are evaluating gene therapy approaches for treatment of some of the medical consequences of excessive alcohol consumption. For example, increasing the amount of superoxide dismutase, an enzyme that metabolizes free radicals in the liver, is one approach for treating alcoholic liver disease. Other encouraging approaches include reducing the activity of TNF-alpha in the liver, developing TNF-alpha antibodies or antisense nucleotides, or reducing other proinflammatory cytokines such as IL-1 and IL-6.

Goal 5: Objectives

Over the next five years, the NIAAA will pursue four objectives in the area of medication development.

Objective 1. Expand research in developing effective medications to suppress the desire to drink.

Objective 2. Expand research into pharmacotherapy for protracted alcohol withdrawal syndrome.

Objective 3. Expand research to identify candidate compounds that can induce sobriety quickly and safely in intoxicated individuals who are experiencing a medical emergency.

Objective 4. Conduct research to explore the role of oxidative stress in alcohol-related organ and tissue damage and test the effectiveness of various antioxidants to prevent, alleviate, or reverse alcohol-associated pathophysiology.

GOAL 6: ADVANCE KNOWLEDGE OF THE INFLUENCE OF ENVIRONMENT ON EXPRESSION OF GENES INVOLVED IN ALCOHOL-ASSOCIATED BEHAVIOR, INCLUDING VULNERABLE ADOLESCENT YEARS AND IN SPECIAL POPULATIONS

Susceptibility to alcoholism results from a complex interaction of genetics and persistent excessive use of alcoholic beverages, with the latter influenced by physiological, psychological, and environmental factors. Studies are now underway to elucidate the relative contribution and/or interaction of these factors in the development of alcoholism. These studies explore heritable characteristics and the influence that environmental factors can exert over time to either promote or impede the development of alcoholism. For example, studies in both humans and animals have found that tolerance and physical dependence can develop over several days of chronic alcohol exposure. This time is also sufficient for changes in gene expression—the process of converting the genetic information encoded in the DNA into the final gene product (i.e., a protein) from specific genes that contribute to alcoholism—to occur.

There is a substantial body of scientific knowledge about the influence of environmental factors (e.g., familial vulnerability and alcohol-related public policies) on alcohol consumption. In comparison, it is only recently that a significant genetic contribution to alcohol-related problems has been documented and appreciated. Moreover, gene-environment interaction studies are costly and often longitudinal.

NIAAA-supported scientists have recently begun to study individual susceptibility to alcoholism during specific stages of postnatal maturation, particularly during adolescence. Of special interest are prospective longitudinal studies of patterns of alcohol consumption, including development of alcohol dependence and mortality and morbidity associated with acute and chronic excess consumption; alcohol craving and appetitive control of drinking behavior involving affect and reinforcement; and negative affect and behavioral undercontrol in childhood, such as impulsivity and stimulus-seeking behavior.

Alcohol remains the most commonly abused substance among adolescents. Given the early onset and frequency of drinking among youth, NIAAA views the impact of alcohol's acute and chronic effects on physiological growth and maturation, as well as its potential deleterious effects on the development of social and interpersonal competencies, as major gene-environment areas of research.

Recent Scientific Advances

There have been relatively few gene-environment interaction studies.

Alcohol Effects on Adolescent Neurobiology

Evidence from human and animal studies indicates that specific neuroanatomical, neurochemical, and behavioral changes occur during postnatal development, much of it influenced by genetics. For example, it has been established that the prefrontal cortex of the brain, an area thought to mediate higher cognitive abilities, undergoes major, pre-programmed changes during adolescence. Support for the postulate that the developing brain may be particularly sensitive to the effects of alcohol is exemplified by a recent study wherein adolescent rats were found to be more sensitive to the memory-impairing effects of acute alcohol administration than were adult rats. Because of ethical and legal limitations in the types of studies that can be conducted with human adolescents, NIAAA-sponsored researchers have developed animal models to investigate gene-environment interactions relevant to adolescent alcohol abuse and alcoholism.

Understanding age-related changes in gene-environment interactions that influence mechanisms of alcohol reinforcement, alcohol preference, or alcohol's subjective effects could be extremely important in understanding the development of alcohol addiction during adolescence.

Genetic and Environmental Precursors to Alcohol-Related Problems

Researchers are developing conceptual models that identify broad personality components as precursors to alcohol-related problems that involve genotype-environment interactions. These interactions are hypothesized to be contributory mechanisms underlying transition from adolescent personality traits to development of alcohol-related problems. Dimensions that have been studied include emotional reactivity, socialization, self-control, and co-occurring disorders (e.g., hyperactivity).

Current environmental influences can include price and availability of alcohol, acute stressors, alcohol dose, taste factors, and reward parameters. Historical influences can include early rearing environment, early stress, and peer influences during adolescence, as well as prior alcohol experience.

Goal 6: Objectives

More basic research is needed in humans and animals to elucidate the interaction of genetics and environmental factors during the period of postnatal maturation.

NIAAA has identified four objectives for the next five years.

Objective 1. Improve understanding of the key parameters in genetic-environmental interactions by conducting longitudinal research studies of high-risk individuals for alcohol-related disorders, with defined genotypes, assessing personality and other psychological traits, biological parameters, and current and past environmental characteristics.

Objective 2. Further develop appropriate animal models, including primates, for adolescent studies.

Objective 3. Develop better statistical models to detect genotype-environment interactions across the lifespan.

Objective 4. Use molecular genetic techniques to study animal models of alcohol-related gene-environment interactions and environmentally-induced changes in gene expression across the lifespan.

GOAL 7: FURTHER ELUCIDATE THE RELATIONSHIPS BETWEEN ALCOHOL AND VIOLENCE

Violence may be defined as behavior that intentionally inflicts, or attempts to inflict, physical harm. As such, it falls within the broader category of aggression, which also includes behaviors that are threatening, hostile, or damaging in a nonphysical way. It has been documented that alcohol consumption is a correlate and possible cause of a significant proportion of violent and aggressive events, including homicides, suicides, physical and sexual assaults, and child abuse, including incest. Interpersonal violence increasingly has become a concern in the U.S. and internationally. The consistency of this association across countries, demographic subgroups, and types of violence, including both extreme cases and the more routine confrontations that occur among community residents, suggests that these findings are not spurious.

In the U.S., alcohol is associated with violence to a far greater extent than all other drugs combined. For example, alcohol is a significant factor in 68 percent of manslaughters, 62 percent of assaults, 54 percent of murders and attempted murders, 48 percent of robberies, and 44 percent of burglaries. Among jail inmates, more than 40 percent of those convicted of rape reported being under the influence of alcohol (or alcohol and other drugs) at the time of the offense. Alcohol use also represents a significant risk factor for domestic violence and is implicated in an estimated 30 percent of child abuse cases. Alcohol consumption has also been found to combine with suicidal conduct, especially among young males, perhaps through its effects on judgment, mood, and impulsive behavior.

The extent to which alcohol causes violence versus simply being associated with violence remains unresolved. Studies in both animals and humans link alcohol more than any other drug with a high incidence of violent and aggressive behavior. Alcohol-related violence is the result of interaction between individual and environmental factors that either promote or inhibit violence. Findings from numerous studies implicate personality, expectancy, situational, and sociocultural factors that may inter-

act with alcohol's pharmacological effects. What is not clear is whether and under what circumstances these interactions may combine to lead to violent episodes.

Researchers are investigating relationships between alcohol consumption and violence in defined populations and for specific types of violence. Although no single model can account for all types of alcohol-related violence, some violent behavior is amenable to treatment and some may be preventable. Of special interest are current studies of (1) intergenerational linkages between alcohol use or abuse and violent behavior; (2) effects of experiencing or witnessing family violence on later alcohol-related behaviors of perpetrators and victims; (3) effects of alcohol on information processing and perception of cues as aggressive (i.e., cognitive impairment); (4) development of alcohol expectancies related to violence (i.e., belief in alcohol consumption as an excuse for violence); (5) effects of laws, policy changes, and police interventions on alcohol-related violence; (6) effects of alcohol treatment on spouse abuse; and (7) role of community norms, neighborhood environments, and alcohol server practices in alcohol-related violence.

Recent Scientific Advances

NIAAA-sponsored research has made significant progress in elucidating the relationships between alcohol and violence. Efforts are now underway to better understand the family and social environments in which violence occurs, examine the potential for cooperation among agencies committed to help, and discover new ways to reduce violence through development of effective prevention programs.

Biology of Alcohol and Violence

Knowledge in the neurobiological aspects of alcohol-related violence has progressed rapidly. Studies based on animal models of alcohol-related aggression implicate brain neurotransmitters (serotonin and GABA) and neurosteroids. Moreover, there is some suggestion of involvement of specific brain areas (basal forebrain). Studies in violent alcoholics suggest predictive utility of low brain serotonin levels and low plasma cortisol levels. These findings suggest potential pharmacotherapies to reduce alcohol-related aggression.

Public Policies and Alcohol-Related Violence

Preliminary evidence suggests that social policies that discourage aggregate alcohol consumption may be effective in reducing rates of violence. These macro-level policies include a variety of alcohol control laws, such as those regulating the number and types of outlets that are permitted to sell alcohol; the minimum legal drinking age for the purchase and consumption of alcohol; and statutes pertaining to server liability. Researchers have found that variations in the stringency of these and other regulations and the vigorousness with which they are publicized and enforced can affect the incidence of violence. Recently, variations in alcoholic beverage prices, which governments can influence via taxation, were found to exert an impact on the prevalence and frequency of child abuse. Other findings imply that an increase in the price of alcohol would reduce violence directed at wives by their husbands.

A significant association has been shown between the minimum legal drinking age and suicide among youths 18 to 20 years of age, suggesting that a lowering of drinking age from 21 to 18 years would increase the number of suicides.

Alcohol and Violence toward Children

Alcohol use is involved in an estimated 30 percent of child abuse cases. Research suggests that associations between alcohol consumption and child abuse or neglect may be a function of chronic alcohol

abuse by the parent/caretaker or intoxication by the perpetrator of abuse at the time of the violent incident. A recent study, which focused on linkages between alcohol consumption and domestic violence, concluded that increasing the cost of alcoholic beverages would reduce violence aimed at children. In addition, the study predicted that laws designed to make obtaining alcoholic beverages more difficult should also be effective in reducing violence against children, i.e., decreasing the number of outlets licensed to sell alcoholic beverages should reduce the likelihood of severe violence. On the other hand, this study also indicated that laws restricting advertisements for alcoholic beverages have been ineffective in reducing violence.

Alcohol and Violence toward Women

Excessive alcohol consumption is frequently a factor in violence toward women. These events range from being the recipient of verbal aggression (for example, hostile or threatening remarks) to battery, rape, and death. Recent findings among women who reported sexual assaults include higher levels of alcohol consumption, both their own and the perpetrator's, and sexual risk-taking behavior. An implication of these findings is that women using alcohol may not recognize assault cues and even if they do, may not be able to respond appropriately when they are inebriated. In addition, women victimized as children or previously assaulted are at increased risk of alcohol abuse and of re-victimization.

Alcohol and Domestic Violence

Domestic violence is a significant problem in the U.S., one in which alcohol consistently emerges as an important factor. Among male alcoholics, 50 to 60 percent or more have been violent toward a woman partner in the year before treatment for alcoholism. Despite evidence that problem drinking and physical assault and battery are associated, there are few studies of the occurrence of domestic violence among alcoholics.

Recently, NIAAA-sponsored investigators have shown that successful treatment for alcoholic husbands that resulted in remission was associated with a six-fold reduction in husband-to-wife violence, returning to levels experienced by nonalcoholic couples in the general population. Results from other research indicate that problem drinking reduces the quality of the marital relationship, even in the early stages of relationship formation. Significant associations have been reported between excessive consumption by the husband, perceptions of marital dissatisfaction, and belief in alcohol as an excuse for aggression.

Goal 7: Objectives

Over the next five years, NIAAA plans to support research that clarifies the relationship between alcohol and violence and, in so doing, assists in rational policy development and in the development of interventions to reduce or prevent alcohol-related violence.

NIAAA will focus on five strategic objectives.

Objective 1. Advance knowledge of the biological and psychosocial processes by which alcohol consumption may lead to escalating aggression and violence.

Objective 2. Increase understanding of the individual and environmental conditions, situations, and circumstances under which alcohol and violence are causally connected.

Objective 3. Increase understanding of the interrelationships among individual-level risk factors (for example, temperament or cognitive ability) and environmental risk factors (for

example, cultural influences or peer expectations) that are associated with alcohol-related aggressive behavior.

Objective 4. Increase understanding of the role of alcohol consumption as a contributing factor to violence in specific high-risk environments, such as bars and gangs, in specific social contexts, such as the family, and the effects of policies designed to reduce or prevent such violence.

Objective 5. Develop and evaluate treatment interventions among individuals who abuse alcohol and have a history of domestic or other violence.

NIAAA CORE STRATEGIES

NIAAA has established nine core strategies for achieving our objectives that will keep the Institute's research enterprise continually directed at advancing the frontier of knowledge across the next five years.

- **Priority Setting.** Continue to seek a productive balance among basic research and research on prevention and treatment initiatives that respond to pressing public health needs, move expeditiously on scientific opportunities as they emerge, and enhance our knowledge base of what works, how, and for whom. Establish and continue to adjust research priorities to ensure scientific progress, meet national needs, and efficiently use the limited resources available to address all goals.
- **Grants Administration and Peer Review.** Maintain effective and efficient grant administration and a high quality of peer review to ensure that only the most meritorious research projects are funded.
- **Management and Supervision.** Ensure that the management and administrative functions necessary to support our mission are carried out effectively and efficiently.
- **Interagency Collaboration.** Continue to work with other Federal agencies to coordinate research opportunities, to partner and reduce duplication of effort, and to share resources, resulting in enhanced effectiveness of programs.
- **Communication of Results.** Communicate scientific results and health information to the alcohol research community, health care providers, patients, policymakers, and the general public.
- **Technology Transfer.** Promote the efficient transfer of new technology forthcoming from NIAAA research to the private sector to facilitate development of new diagnostic tools, drugs and other treatment modalities, and related products with significant public health benefits.
- **Training.** Enhance training programs at the predoctoral, postdoctoral, and early career development levels, especially for underrepresented minorities and women, to ensure an adequate supply of capable individuals in alcohol research.
- **Technical Assistance.** Promote use of the Institute's 15 Alcohol Research Centers as comprehensive technical assistance centers for investigators engaged in multidisciplinary research and as regional education laboratories to assist communities by promoting research on clinical applications.
- **Community Outreach and Education.** Engage schools, postsecondary institutions, colleges, and communities in the development of alcohol awareness and prevention programs, including participation in the National Alcohol Screening Day; creating networks that include educators, employers, and other key stakeholder groups by expanding our public liaison activities; and sponsoring efforts to align prevention policies with new screening methods for assessing problem drinking. Development of an alcohol education module for high school students will be completed and made available for dissemination.

KEY EXTERNAL FACTORS THAT COULD AFFECT ACHIEVEMENT OF THE NIAAA'S GOALS AND OBJECTIVES

NIAAA's Strategic Plan for FY 2001–2005 is predicated upon close partnership with our stakeholders (e.g., scientists, clinicians, and the general public) to advance knowledge of cause, prevention, treatment, and consequence of alcohol abuse and dependence and achieve our mission of improved public health. Some factors, however, that could significantly affect the success of this joint partnership are largely outside of its scope. One of these external factors is:

- **American society's tolerance for alcohol misuse.** Widespread social tolerance for inappropriate alcohol use is a countervailing influence to prevention activities by schools and educators who receive Federal assistance for drug-education and prevention activities.

  NIAAA response: Work with others in the Administration to develop and disseminate the best information available on effective intervention strategies and research findings on the effects of misuse. An example of this would be to make known the finding that early use of alcohol by adolescents leads to a high likelihood of dependence in adulthood. NIAAA will work with Federal leadership to increase the visibility of efforts to discourage tolerance for excessive alcohol use.

LINKING MISSION AND PERFORMANCE MONITORING

NIAAA is committed to being held accountable for measuring and reporting results on our goals and objectives. Preparing a strategic plan that covers a five-year period is an important step. Progress towards achieving the goals and objectives of the plan will be reviewed annually by the NIAAA Director and program staff, the NIAAA Advisory Council, and other expert *ad hoc* advisers. If the prevailing plan's goals and objectives need to be adjusted because of a shift in scientific priorities, the plan will be re-evaluated. NIAAA will also maintain a dialogue with other interested Federal agencies and offices and lay interest groups regarding the strategic plan. In addition, NIAAA will prepare periodic status reports of its activities. These reports will be constructed from the budget justifications and performance "indicators" or measures of success for all NIAAA programs. These reports will include a mix of outcome and intermediate indicators for science advances, both laboratory and patient-oriented, that NIAAA will use during the next five years to judge progress and document results.

Outcome indicators will tell NIAAA whether progress is being made in areas of national need and in the specific goals for its programs. For example, are more children and teens delaying the onset of drinking or engaging in treatment-seeking behavior? Are more medications available that have proved successful in helping problem drinkers achieve and maintain sobriety?

Intermediate indicators will tell NIAAA whether its strategies are working and its programs and management processes are on track, i.e., is the Institute meeting major milestones and deadlines necessary to achieving its goals and objectives?

These basic principles are in keeping with the definitions and guidelines outlined in OMB Circular A-11, Part 2.

USE OF EVALUATIONS AND ASSESSMENTS

In formulating our goals for FY 2001–2005, NIAAA has incorporated findings from major research studies, national assessments, and rigorous internal and external evaluations of our research programs. NIAAA has an active evaluation program that is multi-tiered and culminates with decisions by its Director. Most current evaluations relate closely to the goals and objectives of this plan. Future ones, including secondary analyses of existing data sets and impact assessments of longitudinal studies to help identify "what works," as well as to provide comparative information on program effectiveness, will align even more closely and will fill in knowledge gaps where possible. In addition, data from expert reviews of the quality of NIAAA-funded research and program activities by specially convened Subcommittees of the Institute's National Advisory Council are key sources for strategic directions and indicator data.

For a listing of key documents that provide critical baseline or related data that prospectively inform implementation of NIAAA's goals and objectives, as delineated in the Plan, and support valid and reliable performance measures, see Appendix A.

NIAAA has also drawn upon findings and recommendations of recent external audits of NIH corporate information systems for the daily management of mission-critical NIAAA functions, including tracking systems for administration of research grant, contract, and intramural projects, budget and accounting information, and technology transfer activities. As part of NIAAA's technical transfer activities, the Institute is also working to expand and enhance its public Web presence at *http://www.niaaa.nih.gov*. Lastly, NIAAA has relied upon a body of publications by the U.S. General Accounting Office (GAO) that assess best practices and management techniques for Federal agencies to support and align all elements of its research enterprise to improve the Nation's health.

Drafting the Plan

During much of 1999, drafts of this plan were prepared and circulated within the NIAAA. In turn, senior managers were asked to meet with their staff to discuss the plan, obtain ideas for changes, and also begin to discuss how their offices would implement the plan. The plan reflects input from the scientific and health care communities and interested members of the public. In particular, the National Advisory Council on Alcohol Abuse and Alcoholism and 250 liaison organizations were among those who provided review and comment of the draft. At no time was any contractor involved in the drafting or other development of this Plan.

Appendix: Descriptions of Program Evaluations and Other Studies

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has drawn on a broad range of evaluative information about its programs in preparing this Strategic Plan. For example, the NIAAA National Advisory Council reviews the Institute's research portfolio and provides evaluative advice to the NIAAA Director and senior management several times a year. Council meetings provide an important venue for participation in NIAAA priority-setting by members of the external scientific and consumer advocacy communities. Subcommittees of the Council also review the Institute's research programs by scientific area on a multi-year cycle, and are regularly convened as needed on important topics. NIAAA Division Directors often request reports on program initiatives from outside scientific experts that include assessment of progress toward outcome goals.

In addition to these activities, submitting NIAAA's triennial *Special Report to the U.S. Congress on Alcohol and Health* provides an important mechanism for evaluating the scientific knowledge generated from Institute investments. Lastly, conferences, symposia, and seminars regularly provide opportunities for evaluation and valuable guidance on establishing appropriate performance goals for effective assessment of progress. Information from these formal and informal evaluation processes, coupled with data from other Federal agencies' studies and surveys, where available, influenced the development of NIAAA's key investment strategies and action plans for FY 2001–2005.

Plans for adapting existing practices for assessing NIAAA's administration and management function to the requirements of the Government Performance and Results Act (GPRA) and related management reform activities are currently underway. The Executive Officer; Chief, Financial Planning and Management Branch; and Chief, Information Technology and Management Services Branch are involved in this effort.

Reports

1. Report of the National Advisory Council on Alcohol Abuse and Alcoholism Subcommittee on College Drinking, June 1999.
2. Report of the Research Priorities Subcommittee of the National Advisory Council on Alcohol Abuse and Alcoholism, January 1999.
3. *Bridging the Gap Between Practice and Research: Forging Partnerships with Community-Based Drug and Alcohol Treatment,* Institute of Medicine, National Academy of Sciences (Washington, DC), 1998.
4. *Scientific Opportunities and Public Needs—Improving Priority Setting and Public Input at the National Institutes of Health,* Institute of Medicine, National Academy of Sciences (Washington, DC), 1998.
5. *The Economic Costs of Alcohol and Drug Abuse in the United States—1992,* National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism (Bethesda, MD), 1998.
6. Report of the Subcommittee of the National Advisory Council on Alcohol Abuse and Alcoholism on the Review of the Extramural Research Portfolio for Neuroscience and Behavior, May 1998.

7. Report of the Subcommittee of the National Advisory Council on Alcohol Abuse and Alcoholism on the Review of the Extramural Research Portfolio for Prevention, October 1998.

8. *Ninth Special Report to the U.S. Congress on Alcohol and Health*, June 1997.

9. Report of the Subcommittee of the National Advisory Council on Alcohol Abuse and Alcoholism on the Review of the Extramural Research Portfolio for Fetal Alcohol Syndrome (FAS), May 1997.

10. Report of the Subcommittee of the National Advisory Council on Alcohol Abuse and Alcoholism on the Review of the Extramural Research Portfolio for Genetics, November 1997.

11. *Improving the Delivery of Alcohol Treatment and Prevention Services: A National Plan for Alcohol Health Services Research,* Report of the Health Services Research Subcommittee of the National Advisory Council on Alcohol Abuse and Alcoholism, 1997.

12. *Dispelling the Myths about Addiction: Strategies to Increase Understanding and Strengthen Research,* Committee to Identify Strategies to Raise the Profile of Substance Abuse and Alcoholism Research, Institute of Medicine, National Academy of Sciences (Washington, DC), 1997.

13. Report of the Subcommittee of the National Advisory Council on Alcohol Abuse and Alcoholism on the Review of Utilization and Cost, Financing and Organization, and Effectiveness and Outcomes, 1996.

14. *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment,* Committee to Study Fetal Alcohol Syndrome, Institute of Medicine, National Academy of Sciences (Washington, DC), 1996.

Surveillance Reports

1. *Trends in Alcohol-Related Fatal Traffic Crashes, United States, 1977-96* (Hsiao-ye Yi, Frederick S. Stinson, Gerald D. Williams, and Darryl Bertolucci), December 1998.

2. *Apparent Per Capita Alcohol Consumption: National, State, and Regional Trends, 1977-96* (Gerald D. Williams, Frederick S. Stinson, Lorna L. Sanchez, and Mary C. Dufour), December 1998.

3. *Liver Cirrhosis Mortality in the United States 1970-95* (Forough Saadatmand, Frederick S. Stinson, Bridget F. Grant, and Mary C. Dufour), December 1998.

4. *Trends in Alcohol-Related Morbidity Among Short-Stay Community Hospital Discharges, United States, 1979-95* (M. Fe Caces, Frederick S. Stinson, and Mary C. Dufour), December 1997.

Research Monographs and Other Assessments

1. *1998 Traffic Safety Facts: Alcohol.* National Highway Traffic Safety Administration, U.S. Department of Transportation (compiled annually from the Fatality Analysis Reporting System—FARS), 1998.

2. NIAAA Research Monograph No. 33—*Alcohol Problems and Aging,* NIH Publication No. 98-4163, 1998.

3. NIAAA Research Monograph No. 31—*Alcohol and the Cardiovascular System.* NIH Publication No. 96-4133, 1996.

4. NIAAA Research Monograph No. 32—*Women and Alcohol: Issues for Prevention Research.* NIH Publication No. 96-3817, 1996.
5. NIAAA Research Monograph No. 28—*The Effects of the Mass Media on the Use and Abuse of Alcohol.* NIH Publication No. 95-3743, 1995.
6. NIAAA Research Monograph No. 29—*Stress, Gender, and Alcohol-Seeking Behavior.* NIH Publication No. 95-3893, 1995.
7. NIAAA Research Monograph No. 30—*Alcohol and Tobacco: From Basic Science to Clinical Practice.* NIH Publication No. 95-3931, 1995.

Panels, Seminars, and Symposia

Biomarkers and Surrogate Endpoints: Advancing Clinical Research and Applications, NIH and FDA (Bethesda, MD), April 1999.

Medication Development for Alcoholism: From Laboratory to Patient, NIAAA and ASAM (Bethesda, MD), May 1999.

Visualizing the Future of Biology and Medicine: A Biomedical Imaging Symposium, NIAAA was cosponsor (Bethesda, MD), June 1999.

Early Childhood Neurobehavioral Assessments in Response to Teratogenic Effects: A Focus on Fetal Alcohol Syndrome, NIAAA, in conjunction with NICHD, NIEHS, NINDS, and NIMH (Bethesda, MD), Fall 1999.

Alcohol-Induced Hepatic Fibrosis: Mechanisms, Annual Meeting of the Research Society on Alcoholism, NIAAA (Hilton Head Island, SC), 1998.

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